Partial Translation of Shishido

The effects and pharmacokinetics of rhG-CSF on the treatment of neutropenia in patients with renal failure

Page 974, lines 8-18 in the left column

1) Target

Targets to be tested are 9 renal failure patients with a tendency to pancytopenia. Two of them are conservative renal failure patients having a serum creatinine level of 5.3 and 7.8 mg/dl, respectively, and the remaining 7 patients are under regular hemodialysis (Table 1). As to the cause of pancytopenia, bone marrow aspiration showed hypoplasic findings in Case Nos. 1, 3 and 5, while abdominal CT showed mild splenoma in Case Nos. 4 and 7, suggesting that hypersplenism was responsible for pancytopenia. The cause of pancytopenia in the remaining 4 cases could not be identified. Pre-treatment counts (mean ± SD) of peripheral blood cells were 3500 ± 500/μl for white blood cells, 12.7 ± 2.7 × 10^4/μl for platelets and 269 ± 46 × 10^4/μl for red blood cells.

Page 977, lines 10-16 in the right column

Discussion

Although rhG-CSF has already been clinically tested for treatment of various diseases, there has been no report of its effects and safety in renal failure patients. rhG-CSF is partially metabolized in the liver, but the kidneys are the main organs for its excretion[5]. Thus, this study was conducted for the purpose of clarifying the pharmacokinetics, effects and safety of rhG-CSF in renal failure patients.

Page 979, line 3 from the bottom of the right column to page

Partial Translation of Shishido

980, line 17 in the left column

Summary

rhG-CSF was administered to patients with end-stage renal failure under the schedule of single or two-week consecutive injection to thereby obtain the following conclusions.

1) When administered by single injection, rhG-CSF was found to have a half life of 2.87 hours, which was about two times longer than that in healthy subjects and was not affected by hemodialysis treatment.

2) Marked increases in leukocyte and neutrophil counts and a mild increase in lymphocyte count were observed during single and consecutive administration of rhG-CSF. There was no significant change in other leukocyte differentiations or red blood cell and platelet counts.

3) NAP score increased significantly during single and consecutive administration, and other neutrophil functions also improved in several patients with impaired neutrophil function.

4) Slight bone pain and an increase in serum alkaline phosphatase were observed in about a half of the patients during consecutive administration of rhG-CSF. Neither antibody nor accumulation of rhG-CSF was noted.

5) In view of the foregoing, rhG-CSF was considered to be an effective and safe therapeutic agent for neutropenia and neutrophil dysfunction in patients with renal failure. In addition, 50 $\mu g/m^2$ of rhG-CSF may be adequate as an initial dose for patients with renal failure.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL
OF COPIES OF TRANSLATION
OF THE INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY
(CHAPTER I OR CHAPTER II
OF THE PATENT COOPERATION TREATY)
(PCT Rules 44*bis*.3(c) and 72.2)

To:

SHAMOTO, Ichio
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2006. 7. 31

Date of mailing *(day/month/year)*	
20 July 2006 (20.07.2006)	
Applicant's or agent's file reference YCT-970	IMPORTANT NOTIFICATION
International application No. PCT/JP2004/015127	International filing date *(day/month/year)* 14 October 2004 (14.10.2004)
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA et al	

1. **Transmittal of the translation to the applicant.**

☐ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).

☑ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

2. **Transmittal of the copy of the translation to the designated or elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

EP, KR

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. **Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yoshiko Kuwahara
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TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
YCT-970		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/015127	14.10.2004	14.10.2003
International Patent Classification (IPC) or national classification and IPC		
A61K38/18, A61P3/10, 9/10, 13/12		
Applicant		
CHUGAI SEIYAKU KABUSHIKI KAISHA		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/015127

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following _____ which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/015127

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 10

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

The subject matter of claim 10 relates to methods for treatment of the human body by therapy. Thus, this International Preliminary Examining Authority is not required to carry out international preliminary examination on this subject matter under the provisions of PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 10

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/015127

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9	YES
	Claims		NO
Inventive step (IS)	Claims	1-9	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: Kanji Shishido et al., Nichijinshi, 1991, Vol. 33, No. 10, pages 973 to 981

Document 2: Akiko Saeki, Nichijin Kaishi, 1996, Vol. 38, No. 12, pages 584 to 595

Document 3: Strutz, F. et al., Nephron, 1995, Vol. 69, No. 4, pages 371 to 379

Claims 1 to 9

The invention set forth in claims 1 to 9 is not disclosed in any of the documents cited in the international search report, and is therefore novel and involves an inventive step.

In particular, documents 1 to 3 neither disclose nor suggest that G-CSF promotes the repair and regeneration of kidney tissue, and is effective in the treatment of renal failure.